MALARIA VACCINE

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a 35 U.S.C. §371 U.S. national entry of International Application PCT/US2009/004243 (WO 2010/036293) having an International filing date of Jul. 22, 2009 which claims the benefit of U.S. Provisional Application No. 61/099,651, which was filed on Sep. 24, 2008, the entire contents of which are incorporated herein by reference.

BACKGROUND OF THE INVENTION

Malaria is one of most dangerous infectious diseases in tropical and subtropical countries, afflicting about 300 million people. The pathogen of the disease is a protozoan parasite, *Plasmodium* sp. which is transmitted by *Anopheles* mosquitoes. Four species of malaria parasites can infect humans under natural conditions: *Plasmodium falciparum, P. vivax, P. ovale*, and *P. malariae. P. falciparum* and *P. vivax* cause the most infections worldwide.

P. falciparum is the agent of severe, potentially fatal malaria. Malaria caused by *P. falciparum* is responsible for nearly 1 million deaths annually. Based on recent estimates from the WHO, worldwide, there were an estimated 247 million malaria cases among 3.3 billion people at risk living in 109 countries [1]. Infections caused by *P. falciparum* and *P. vivax* account for more than 90% of global malaria burden; the former being responsible for nearly all the deaths due to malaria, nearly a million deaths of children under 5 years [2]. Among the current efforts against malaria include increasing use of insecticide treated bed nets and use of combination drugs to tackle the problem associated with drug resistance. The emergence of drug-resistant strains over the last 4 decades has underscored the necessity for improved control strategies. Accordingly, the development of a safe and effective malaria vaccine will be an important step towards controlling malaria. Vaccine development efforts to date have focused on candidate antigens represented in the pre-erythrocytic, erythrocytic and sexual stages of the parasite. Currently, the only vaccine advanced in clinical development, RTS,S, has shown partial protection against infection and disease severity in several clinical trials [6,7].

Immunity against the sexual stages of the parasite offers an effective way to reduce or stop malaria transmission and in that respect offers the greatest promise towards the goal of progressively eliminating malaria from endemic countries. A transmission blocking vaccine (TBV) [8] specifically targeting the sexual development of the parasite in the mosquito vector may elicit immunity which can effectively block transmission of the parasite from invertebrate mosquito vector to vertebrate host. Transmission of malaria depends upon the presence of infectious male and female gametocytes in the peripheral blood of infected persons and successful ingestion of these gametocytes by *Anopheles* mosquitoes. Soon after ingestion, exflagellation occurs within the mosquito midgut, and emergent male gametes fertilize female gametes, resulting in the formation of zygotes. The zygotes undergo post-fertilization transformation into motile ookinetes which traverse the midgut epithelium and develop into oocysts resulting in the production of infective sporozoites. Finally the sporozoites are released into the hemocoel, invade the salivary glands and are transmitted to vertebrate hosts during subsequent blood feeding [9].

The targets of transmission blocking antibodies include pre-fertilization antigens (Pfs230 and Pfs48/45) expressed in the circulating gametocytes and post-fertilization antigens (Pfs25 and Pfs28) expressed during mosquito stage ookinete development [10]. Unlike Pfs25 and Pfs28, pre-fertilization antigens are also targets of the natural immune response and thus immunity induced by a vaccine based on any of these antigens will have the added benefit of natural boosting of immunity. To date, only Pfs25 and Pvs25 (*P. vivax* homolog of Pfs25) have undergone limited Phase I clinical trials with marginal success [11,12]. It has not been possible to evaluate any of the pre-fertilization antigens as vaccines simply because they have not been available in sufficient quantity and proper protein conformation.

Although much progress has been made in the recent past, the development of a safe, effective and affordable malaria vaccine has remained a challenge. A vaccine targeting sexual stages of the parasite will not only reduce malaria transmission by female *Anopheles* mosquitoes, but also reduce the spread of parasites able to evade immunity elicited by vaccines targeting pre-erythrocytic and erythrocytic asexual stages.

SUMMARY OF THE INVENTION

As described below, the present invention features immunogenic compositions based on pre-fertilization antigens expressed in the circulating gametocytes in the peripheral blood of infected persons. The present invention makes use of an approach that harmonizes codon usage frequency of the target gene with those of the expression host for heterologous expression of protein. Taking these concepts into account, an algorithm termed "codon harmonization" [19] was developed where synonymous codons from *E. coli* were selected that closely resemble the codon usage of a native pre-fertilization gene, for example the native Pfs48/45 gene, including regions coding 'link/end' segments of proteins in *P. falciparum.*

Also featured in the invention are antibodies, and methods to prevent the transmission of malaria using the immunogenic compositions of the invention.

In a first aspect, the invention features a method of blocking transmission of *Plasmodium falciparum* or *Plasmodium vivax* in a subject comprising administering to a subject an immunogenic composition comprising one or more *Plasmodium falciparum* or *Plasmodium vivax* pre-fertilization antigens, thereby blocking transmission of *Plasmodium falciparum* or *Plasmodium vivax* in the subject.

In another aspect, the invention features a method of immunizing a subject against *Plasmodium falciparum* or *Plasmodium vivax* comprising administering to a subject an immunogenic composition comprising one or more *Plasmodium falciparum* or *Plasmodium vivax* pre-fertilization antigens, thereby immunizing the subject against *Plasmodium falciparum* or *Plasmodium vivax.*

In still another aspect, the invention features a method for treating or preventing malaria in a subject comprising administering to a subject an immunogenic composition comprising one or more *Plasmodium falciparum* or *Plasmodium vivax* pre-fertilization antigens, thereby preventing malaria in the subject.

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